communication. The method includes supplying the sample into a first chamber, performing a first reaction in the first chamber, moving the sample from the first chamber to the second chamber, and performing a second reaction in the second chamber, wherein the second reaction is different from the first reaction, and wherein the first or the second chambers are selected from the group of chambers adapted to perform a preparative reaction, an analysis reaction including hybridization, sample acquisition, DNA extraction, amplification, IV transcription or labeling. The method also includes performing confocal microscopy on the hybridized sample by detecting an optical signal from the hybridized sample inside of the chamber using a reader device located outside of the chamber; receiving a signal output from the reader device; and analyzing the signal output with a digital computer to indicate a property of the sample based on the confocal microscopy.

In US Patent 5,587,128, Wilding does not disclose or suggest using confocal microscopy or anything similar. In col. 19, lines 16 through 37, Wilding discloses the following:

> The analytical devices also may be utilized in combination with an appliance for viewing the contents of the mesoscale channels in the devices. The appliance in one embodiment may comprise a microscope for viewing the contents of the mesoscale channels in the devices. In another embodiment, a camera may be included in the appliance, as illustrated in the appliance 60 shown schematically in FIGS. 17 and 18. The appliance 60 is provided with a housing 62, a viewing screen 64 and a slot 66 for inserting a device into the appliance. As shown in cross section in FIG. 18, the appliance 60 also includes a video camera 68, an optical system 70, and a tilt mechanism 72 for holding device 10, and allowing the placement and angle of device 10 to be adjusted manually. The optical system 70 may include a lens system for magnifying the channel contents, as well as a light source. The video camera 68 and screen 64 allow changes in sample fluid properties, such as flow properties or color, induced by the presence of polynucleotide amplification product, to be monitored visually and optionally recorded using the appliance. Additionally, addition or removal of fluid samples to and from the reaction chambers may be monitored, e.g., optically, using the appliance. (Emphasis ours)

Therefore, US Patent 5,587,128 to Wilding alone cannot anticipate claim 80, or cannot render claim 80 obvious.

Furthermore, US Patent 5,587,128 to Wilding in combination with US Patent 5,424,187 to Fodor does not render claim 80 obvious. Wilding discloses using a microscope for viewing the contents of the mesoscale channels in the devices. As claimed in claim 80, the present invention recites performing confocal microscopy on the hybridized sample by detecting an optical signal from the hybridized sample inside of the chamber. While US Patent 5,424,187 to Fodor et al teaches confocal microscopy, it does not disclose performing confocal microscopy on the hybridized sample by detecting an optical signal from the hybridized sample inside of the chamber. There is no suggestion that confocal microscopy can be performed inside the chamber. Therefore, claim 80 is patentable over US Patent 5,587,128 to Wilding in combination with US Patent 5,424,187 to Fodor. The use of the Schinpelsky reference does not render claim 80 in any way obvious.

Applicants refer the Examiner to the personal interview held with Mr. Sherr on August 15, 2001. As shown in the interview summary, the present application clearly teaches confocal microscopy as claimed in claim 80 (and claim 93). Based on the interview, Applicants representative was under the impression that these claims were patentable over US Patent 5,587,128 to Wilding alone or in combination with US Patent 5,424,187 to Fodor.

In this amendment, Applicant introduced further dependent claims directed to performing confocal microscopy on a probe array inside the chamber, or performing scanning confocal microscopy on the sample inside the chamber. None of these features in combination with independent claim 80 (or claim 93) is disclosed in the prior art of record.

When rejecting independent claims 80 or 93 over US Patent 5,587,128 to Wilding alone or in combination with US Patent 5,424,187 to Fodor, the Examiner stated:

> Wilding et al column 19, teaches the use of magnifying lenses so to aid in the detection of results in microchannels. The use of such magnification and detection means is considered to meet the limitation of confocal microscopy. In the event that such does not meet the limitation of confocal microscopy, the rejection of all of the above-identified claims, sans claim 84, is still applicable, as the aspect of performing confocal microscopy is not required. In support of this

> position, attention is directed to claims 80, 93, and 106, the three independent claims currently before the Office. In each instance a group of alternative processes are listed and identified, in the alternative, as being performed in "at least two chambers." Even if Wilding et al, the use of such detection means would have been obvious to one of ordinary skill in the art at the time the invention was made, especially in light of the very nature of the size of the devices which Wilding describes as being "mesoscale." And even if such would not have been obvious by the teachings of Wilding et al alone, it would have been obvious in view of the teachings of Fodor et al (US Patent 5,424,186) which teaches explicitly of the use of confocal microscopy.

Applicants respectfully disagree with this statement. First, as reproduced above, Wilding mentions the use of microscopy for viewing contents of his mesoscale channels. There is no teaching or suggestion regarding confocal detection. Second, as a separate embodiment, Wilding discloses a camera with a video camera, optical system, ..., and magnifying lenses to aid in the detection of results in microchannels. However, these elements are not sufficient to perform confocal microscopy. There is nothing in the teaching of Wilding to suggest a person of ordinary skill in the art to use confocal microscopy. The Examiner stated due to the use of "mesoscale" microchannels confocal microscopy would have been obvious or at least provide some suggestion to combine with Fodor. However, there is no absolutely evidence to support such statements.

Applicants strongly believe that, if anything, the use of "mesoscale" microchannels perhaps would lead a person of ordinary skill in the art away from confocal microscopy, and away from any combination with the teaching of US Patent 5,424,187 to Fodor. In US Patent 5,424,187 Fodor does not use mesoscale" microchannels. Certainly, the use of mesoscale" microchannels would lead a person of ordinary skill in the art away from using probe arrays, as now claimed in dependent claims 110 and 114.

Importantly, Applicants note that both claims 80 and 93 include positive recitations of performing confocal microscopy on the hybridized sample by detecting an optical signal from the hybridized sample inside of the chamber using a reader device located outside of the chamber and analyzing the signal output with a digital computer to indicate a property of the sample based on the confocal microscopy.

Therefore, these recitations are clear claim limitations regardless of any additional alternative claim limitations.

As claimed in claim 106, the invention is a method of analyzing a sample in an integrated microfluidic device. The method includes supplying the sample into a first chamber and moving the sample from the first chamber to a second chamber by employing a valve located in a channel between the first chamber and the second chamber, wherein the first chamber and the second chamber is selected from the group consisting of a chamber adapted to perform a preparative reaction, an analysis reaction, sample acquisition, DNA extraction, amplification, IV transcription or labeling. The method also includes receiving a signal output from a reader device and indicating a property of the sample.

Importantly, Wilding does not disclose a valve located between two of two chambers, as claimed in independent claim 106 (or independent claim 107). While Wilding discloses least two reaction chambers and a sample that is caused to move from one reaction chamber to another, as pointed out by the Examiner, Wilding does not disclose a valve located between two reaction chambers. Specifically, in col. 23 lines 35 through 40 (and at another places), Wilding discloses:

> The appliance 50 is provided with flow paths 56 mated to ports 16A, 16B, 16C, and 16D in device 10. The appliance also includes valves that allow the ports 16A, 16B, 16C and 16D to be mechanically opened and closed. Port 16E is included for adding reagents to detection chamber 22C.

Thus, Wilding discloses a valve at the input port into his device and not a valve located between two reaction chambers. This is an important patentable difference between Wilding and the invention as claimed in dependent claim 106. Dependent claims 120 and 124 include the valve limitation and additional novel combination of features recited in the independent claims 80 and 93, respectively.

The above-described differences are more than enough to distinguish patentably independent claims 80, 93, 106 or 107 over the above-discussed patents, or any other prior art of record. The dependent claims include additional novel combination of

features. Accordingly, all pending claims are now in condition for allowance and such action is respectfully requested.

Please charge any fees or apply credits to the Deposit Account No. 01-0431.

Respectfully submitted,

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March 6, 2002

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Attorney Docket 1087(A1-35US3)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Art Unit : 1655
Examiner : Bradley L. Sisson

Applicant: ROBERT J. LIPSHUTZ et al.
Serial No.: 09/519,148
Filed : March 6, 2000

Title : INTEGRATED NUCLEIC ACID DIAGNOSTIC DEVICE

Amendments
With changes shown

80. (Three times amended) A method of analyzing a sample in an integrated microfluidic device having at least two chambers in fluid communication, comprising:

supplying the sample into a first chamber of the integrated microfluidic device, wherein the first chamber is selected from the group of chambers adapted to perform a preparative reaction, an analysis reaction, sample acquisition, DNA extraction, amplification, IV transcription or labeling;

performing a first reaction in the first chamber;

moving the sample from the first chamber to the second chamber, wherein the second chamber is selected from the group of chambers adapted to perform a preparative reaction, an analysis reaction including hybridization, sample acquisition, DNA extraction, amplification, IV transcription or labeling;

performing a second reaction in the second chamber, the second reaction being different from the first reaction; [and]

performing confocal microscopy on the hybridized sample by detecting an optical signal from the hybridized sample inside of the chamber using a reader device located outside of the chamber;

receiving a signal output from the reader device; and

analyzing the signal output with a digital computer to indicate a property of the sample based on the confocal microscopy.

93. (Three times amended) A method of analyzing a sample in an integrated microfluidic device having at least three chambers in fluid communication, comprising:

supplying the sample into a first chamber of the integrated microfluidic device, wherein the first chamber is selected from the group of chambers adapted to perform a preparative reaction, an analysis reaction, sample acquisition, DNA extraction, amplification, IV transcription or labeling;

performing a first reaction in the first chamber;

moving the sample to the second chamber, wherein the second chamber is selected from the group of chambers adapted to perform a preparative reaction, an analysis reaction including hybridization, sample acquisition, DNA extraction, amplification, IV transcription or labeling;

performing a second reaction in the second chamber, the second reaction being different from the first reaction;

moving the sample to the third chamber, wherein the third chamber is selected from the group of chambers adapted to perform a preparative reaction, an analysis reaction, sample acquisition, DNA extraction, amplification, IV transcription or labeling;

performing a third reaction in the third chamber, the third reaction being different from both the first and second reactions;

performing confocal microscopy on the hybridized sample by detecting an optical signal from the hybridized sample inside of the chamber using a reader device located outside of the chamber;

receiving a signal output from the reader device; and

analyzing the signal output with a digital computer to indicate a property of the sample.